Nasal Eosinophilia in Allergic and Nonallergic Rhinitis: Usefulness of the Nasal Smear in the Diagnosis of Allergic Rhinitis

David M. Lans, D.O., Norma Alfano, B.S., and Ross Rocklin, M.D.

ABSTRACT

Diagnostic nasal cytology has been advocated for use in distinguishing allergic from nonallergic rhinitis. We sought to determine prospectively the frequency of nasal eosinophilia (NE) in 100 patients in whom having allergic rhinitis (AR), nonallergic rhinitis, and other atopic conditions not involving the respiratory tract have been diagnosed. A nasal smear was obtained from consenting adults using the Rhino-Probe curette. Patients taking local or systemic corticosteroids, those with chronic rhinitis associated with aspirin sensitivity, and those with sinusitis were excluded. All cytograms were coded and read by a single "blinded" investigator. NE was considered significant if >20% of sampled cells were eosinophils. Twenty-six of 61 (43%) patients with AR had NE. No NE was detected in the control population or in the skin test negative group of patients in whom having nonallergic rhinitis was diagnosed. One of 16 patients with allergic disease not involving the respiratory tract exhibited NE; this patient had atopic dermatitis with peripheral eosinophilia. No cases of eosinophilic nonallergic rhinitis were detected. There was no significant correlation of symptoms or the number of positive skin tests with NE. These data suggest that the nasal smear for eosinophils is an insensitive but specific test for the diagnosis of allergic rhinitis, when patients with nasal polyposis and aspirin sensitivity and/or negative skin tests are excluded.

New England Medical Center, Department of Medicine, Division of Allergy, Boston, MA

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Correspondence to David M. Lans, D.O., Albert Einstein College of Medicine, 1165 Morris Park Ave., Bronx, NY 10401

The nasal cytogram is often used as an aid in the diagnosis of rhinitis.[1-8] It has been cited as a means to distinguish allergic from nonallergic causes of rhinitis in patients whose history, physical examination, and skin test results are equivocal.[5,7,9] The presence of eosinophils in nasal secretions or direct nasal smears classically suggests the diagnosis of allergic rhinitis. However, the recent recognition of eosinophilic nonallergic rhinitis[1,4,10] and the frequent association of nasal eosinophilia in nonallergic, perennial rhinitis with polyposis and aspirin sensitivity[11] have complicated the interpretation of the nasal smear. The presence of increased amounts of other cell types, including basophils and mast cells, is also variably associated with allergic upper respiratory disease.[6,8,12] Since there is no "gold standard" for the diagnosis of allergic rhinitis, we asked whether the addition of nasal cytology to the initial diagnostic evaluation of patients with rhinitis might be helpful for clinicians faced with uncertainty in diagnosis.

Several investigators have studied nasal cytology in relation to various upper respiratory diseases.[4,10-12] However, the only prospective studies evaluating the diagnostic utility of the nasal smear in allergic rhinitis

have been performed in children.[5,6,13] In order to document further the clinical utility of the nasal smear for eosinophils in allergic respiratory disease, we sought to determine prospectively the frequency of nasal eosinophilia (NE) in adult patients in whom allergic rhinitis (AR), nonallergic rhinitis, and other atopic conditions not involving the upper respiratory tract are diagnosed. One hundred ten adult allergy clinic patients were studied from August 1986 through March 1987. We sought to determine the specificity and sensitivity of the test in the diagnosis of AR, as well as to survey the frequency of the ENR syndrome.

METHODS

Patient Selection

One hundred ten adult patients, 59 women and 51 men ranging in age from 19 to 72, presenting to the Tufts-New England Medical Center allergy clinic for evaluation were studied (Table I). All patients were informed of the purpose of the study and the nasal smear procedure, and provided their consent. Patients who were taking local or systemic corticosteroids were excluded, as were patients with chronic rhinitis with polyposis and/or aspirin sensitivity. Ten adult male and 8 female volunteers (age range 25–55) who reported no history of allergic disease or rhinitis served as control subjects.

Clinical Evaluation

All patients were evaluated with complete history and physical examinations and skin testing by allergy clinic personnel. In addition, paranasal sinus radiographs, complete blood counts, and/or nasal cultures were obtained if sinusitis or polyposis was suspected clinically. The latter patients complained of atypical symptom patterns, including persistent nasal congestion or obstruction, anosmia, purulent discharge, facial pain, fevers, and headache. Nasal mucosal examinations were performed with specula. Fiberoptic rhinoscopy was not employed. Participating allergy clinic physicians were asked to complete a data base sheet indicating patient characteristics, the results of their findings, and the clinical diagnosis.

Skin testing was performed on all patients initially by the prick testing method using a panel of aeroallergens common to the New England region. All negative prick tests were repeated with intradermal testing. Skin test results were considered to be positive if either the prick or intradermal reactions were detected.

Diagnostic Considerations

A diagnosis of allergic rhinitis was made if the history and physical findings correlated with positive skin test results. These patients typically complained of sneezing, nasal irritation, and itching with watery rhinorrhea often in a seasonal pattern, or in relation to specific environmental exposure (such as animal dander). Skin test-negative patients with persistent symptoms (typically nasal congestion, rhinorrhea, and postnasal drip) were considered to have chronic nonallergic rhinitis if nasal polyposis, obstruction, and sinusitis were satisfactorily ruled out by the methods described above. Included in this group were patients with typical vasomotor symptoms. In some cases, patients with perennial or intermittent symptoms were found to have positive skin test results that were felt by their physician to be irrelevant. These patients were also considered to have chronic nonallergic rhinitis.

A number of patients in our clinic population were observed to have perennial symptoms of nasal congestion, sometimes in association with sneezing and nasal irritation, who had skin test reactions only to dust and/or *Dermatophagoides farinae* allergens. We elected to group and consider these patients separately because it was difficult to determine clinically if their symptoms were allergic in etiology.

Patients with asthma with and without rhinitis were included; all underwent spirometry and skin testing. Other allergy diagnoses included those not involving the upper respiratory tract: stinging insect allergy, urticaria, food allergy, and atopic dermatitis.

Patients taking intranasal or systemic corticosteroids were excluded from the study. If nasal polyps were observed on physical examination, these patients were also excluded. A diagnosis of acute sinusitis was made if the patient had features of sinus tenderness, purulent secretions, hyperemic mucosa, a brief duration of ill-

TABLE I

Patient Characteristics

	No.	Male	Female	Age Range	Mean Age
Allergy clinic patients	92	43	49	18–72	37
Control subjects	18	8	10	25–55	33
Total	110	51	59	18–72	34

ness, and/or "positive" sinus radiographs. A diagnosis of chronic sinusitis rested on the presence of persistent symptoms, nasal and postnasal discharge, headaches, and "positive" radiographs. These patients were also excluded from the study.

Nasal Smear Technique

All specimens were obtained by gently scraping the inferior aspect of the inferior nasal turbinate with the Rhino-Probe (Symbiotic Corporation, San Diego, CA) curette under direct visualization. The Rhino-Probe is a semirigid plastic device of about 12 cm in length with a 3-mm curette tip. Any similar curette device that is small enough to enter the nasal vestibule and obtain a mucosal scraping from the inferior nasal turbinate is satisfactory. It is important to obtain a scraping, not merely a sampling, of surface mucosal secretions so that an adequate cell sample is obtained. Sampled material was smeared on glass slides and duplicate specimens were immediately fixed in 95% ethanol for 30 seconds. The cytograms were coded randomly prior to staining and microscopy. Specimens were stained with an automated Wright-Geimsa staining device. All cytograms were read and scored by a single microscopist. Multiple high-power fields were scanned on both slide samples. All cells present, representing a mixture of epithelial cells and cells in secretions, were counted. Nasal eosinophilia was considered to be present of >20% of the cell population consisted of eosinophils.[2,7,10] This measure is preferred to the 0 to 4+ grading system used by some investigators because it is more objective and reproducible. After scoring, the code was broken and nasal smear results were compared with data base sheets.

Analysis of Data

The diagnostic sensitivity, or true-positive rate, in detecting allergic rhinitis was determined by dividing the number of patients with clinically diagnosed AR and negative nasal smears (false negatives; FN) by the sum of AR patients with NE (true positives; TP) and without NE (FN). The diagnostic test specificity, or true-negative rate, was determined by dividing the total number of subjects without AR (true negatives; TN) by the sum of all patients without AR (TN) and those without AR but with positive nasal smears (false positives; FP). The predictive value positive and the predictive value negative were also assessed, using the standard formulas: TP/(TP + FP) and TN/(TN + FN), respectively. A one-variable chi-square analysis of all groups evaluating the presence of NE in subjects with and without AR and which included Yates' correction test was used to demonstrate statistical significance of the data.

RESULTS

The diagnosis of AR was usually easily made when history, physical examination, and skin test results correlated. Sixty-one patients fell into this group (Table II); 26 of these had NE (43%). None of the 18 control subjects had NE. None of the 11 patients with vasomotor or chronic nonallergic rhinitis had NE. Fourteen patients with perennial symptoms had skin test reactions only to house dust and/or *D. farinae* extracts. Six patients in this group were felt by their physicians to clearly have AR based on the nature of their symptoms and its relation to antigen exposure. Two of these patients had positive nasal smears. The remaining eight dust or mite antigen skin test reactive patients were felt to possibly have AR related to these allergens; none of

TABLE II

Nasal Eosinophilia Results

Diagnosis	No. of Patients	No. with NE	% with NE
Allergic rhinitis	61	26	43
Chronic, nonallergic rhinitis	11	0	0
Chronic rhinitis with skin reactivity only to dust and/or mite antigens	14	2	14
Other allergic disease	12	1	8
Control patients	18	0	0
Asthma with rhinitis	13	5	38
Asthma without rhinitis	4	0	0
Total number of patients sampled	110	27	25

TABLE III

Lack of Correlation between Presence of Acute Symptoms and Nasal Eosinophilia in Patients with Allergic Rhinitis

	Patients with Symptoms*	Patients without Symptoms
No. of patients	47	14
NE present (%)	20 (43)	6 (43)
NE absent (%)	27 (57)	8 (57)

* *Symptomatic patients included those who reported sneezing, rhinorrhea, itchy nose, nasal congestion, or postnasal drip at the time the nasal smear was taken.*

this group exhibited NE. Twelve patients had allergic conditions not involving the upper respiratory tract. These patients presented with urticaria, food allergy, asthma without rhinitis, atopic dermatitis, and stinging insect allergy. Only one patient, with atopic dermatitis and peripheral eosinophilia, had NE.

Forty-seven of the patients with AR were symptomatic at the time the nasal smear was taken (Table III). Twenty (43%) of these patients exhibited NE. Thus, the frequency of NE in symptomatic and asymptomatic AR did not differ from that in the group of AR patients as a whole. Asthmatics were no more likely to exhibit NE than patients without asthma. NE was not observed in asthmatics without rhinitis.

As shown in Table IV, the nasal smear for eosinophils was a highly specific test in the population studied (98%), with a similarly high positive predictive value (96%). However, the test is insensitive (43%) and has a low negative predictive value (58%). Chi-square analysis indicated $p < 0.001$.

DISCUSSION

Nasal eosinophilia has been reported to occur in allergic rhinitis, perennial nonallergic rhinitis with nasal polyps and aspirin sensitivity, and nonallergic rhinitis with eosinophilia.[1-5,8,9,11,13,14] Generally, the diagnosis of allergic rhinitis is easily made on the basis of history and physical examination and skin test or radioallergosorbent test (RAST). However, in some patients, particularly those with chronic rhinitis, it may be difficult to clearly implicate an allergic etiology. As many as 35% of the general adult population may have positive skin tests[15]; therefore, without a strong clinical correlation, positive skin tests may be difficult to interpret.

It is important to distinguish between allergic and nonallergic causes of rhinitis because the decision to institute allergen immunotherapy and/or undertake specific environmental controls as well as specific drug therapy rests largely upon this assessment. The nasal smear for eosinophils is a potentially useful test if it helps to distinguish allergic from nonallergic disease.

The cells of the nose can be sampled by two common methods: examination of nasal secretions obtained by having the patient expel nasal secretions into wax paper from which a smear is stained and microscopically studied; and direct mucosal cell sampling by scraping or curettage of nasal mucosa, followed by cytogram preparation. Both techniques yield an adequate cell sample for analysis, but the relative cell composition may vary thus yielding differing results. Investigators have used both methods in their cytologic studies, but both methods have not been directly compared. We chose to use the curettage method in our study for several reasons. By directly sampling cells obtained from the nasal turbinate mucosa, contamination by cells of the anterior vestibule could be avoided. This anterior portion of the nares generally contains neutrophils, epithelial cells, and other phagocytic and inflammatory cells and does not necessarily reflect the state of health of the patient.[5,6,8] A mucosal smear, on the other hand, directly sampled from the posterior, inferior turbinate provides cells that are present at the location of allergic, inflammatory, and other reactions leading

TABLE IV

Nasal Eosinophilia in Allergic Rhinitis: Data Analysis*

Sensitivity (true positive rate)	TP/(TP + FN)	43%
Specificity (true negative rate)	TN/(TN + FP)	98%
Predictive value positive	TP/(TP + FP)	96%
Predictive value negative	TN/(TN + FN)	58%
Chi-square analysis		$p < 0.001$

* *TP (True positive): AR patients with NE (26).*
TN (True negative): patients without AR and without NE (48).
FP (False positive): patients without AR and with NE (1).
FN (False negative): patients with AR and without NE (35).

to rhinitis, and thus reflects more closely the cytology present at the site of pathology.

In the present study, NE was present in 43% of patients with AR. This finding is similar to that of Mullarkey et al.[4] in their classic study of eosinophilic nonallergic rhinitis (ENR), in which 41% of patients with AR had NE. This low sensitivity suggests that the nasal smear is of limited usefulness in detecting an allergic cause of rhinitis. However, only one patient (atopic dermatitis) had NE in the absence of AR, indicating a diagnostic specificity of 98% and a positive value predictive of 96% in our group. While repetitive sampling of nasal mucosal smears might be expected to yield a greater prevalence of NE, we elected to include in our study only the information derived from duplicate samples obtained during the initial patient visit. This approach should reflect the test's usefulness as part of the initial diagnostic evaluation of patients with upper respiratory symptoms, and its practicality in the office or clinic setting. By excluding patients with rhinitis and polyposis (a diagnosis that is readily made by history and physical examination and which is expected to demonstrate NE in as many as 88% of patients[11]), the presence of NE strongly suggests a diagnosis of AR. No patient with classic vasomotor rhinitis had NE.

We did not identify any patients with ENR. The frequency of ENR in relation to other causes of rhinitis is not clear. Mullarkey et al.[4] reported a 15% prevalence in a sample of 142 patients. However, one-third of the ENR group had polyposis and 52% had sinusitis. These types of patients were excluded from our study. Jacobs et al.[10] in a study of the immunologic parameters present in ENR clearly excluded patients with nasal polyps and aspirin sensitivity and those with evidence of allergy on the basis of skin test or RAST. However, the overall frequency of ENR in their patient population was not determined. Still, the discrepancy between our findings and those of Jacobs et al. remains unclear. Perhaps ENR relates to environmental factors; its prevalence may differ in patient populations from different geographic locations. Patients with ENR, by definition, have negative skin tests. Thus, patients with positive skin tests and clinically ambiguous symptoms are very likely to have AR if NE is present. On the other hand, only a limited number of patients with AR can be expected to demonstrate NE, at least when sampled on a single occasion.

Some patients with chronic rhinitis are symptomatic following exposure to perennial allergens such as dust, mite, or some molds. Since up to 35% of all patients will have clinically irrelevant skin test reactions, it may be difficult to establish an allergic etiology in the group of patients with persistent or frequent symptoms of rhinitis and positive skin tests to one or more of these antigens. We see a substantial number of patients in our clinic population who have skin test responses to dust and/or mite extracts alone. We therefore decided to evaluate this group separately. The 14% incidence of NE in these patients contrasts with the overall group of AR patients, in whom NE was observed in 43%. This suggests that some of these patients with chronic rhinitis have an allergic etiology, while in others the skin tests are irrelevant. The nasal smear is thus useful in identifying at least some of the patients in this ill-defined group who may have AR. This may have important implications for patient management and the decision to institute specific immunotherapy.

CONCLUSION

The nasal smear for eosinophils is a simple, well-tolerated test that provides rapid results. It has a low diagnostic sensitivity (43%) but is specific for the diagnosis of allergic rhinitis when patients with chronic rhinitis associated with nasal polyposis, aspirin sensitivity, or sinusitis are excluded, as well as those receiving systemic or local corticosteroids. In the patient with positive skin test or RAST, whose rhinitis is possibly allergic, the presence of nasal eosinophilia strongly supports the diagnosis of allergic rhinitis. However, a negative nasal smear for eosinophils does not rule out the diagnosis. Analysis of other cells present in the cytogram, such as mast cells, basophils, and goblet cells, may also provide valuable diagnostic information. We have not addressed this in the present study; however, future investigations in this area are likely to be informative.

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